ROPES & GRAY LLP
ONE INTERNATIONAL PLACE BOSTON, MA 02110-2624 617-951-7000 F 617-951-7050
BOSTON NEW YORK PALO ALTO SAN FRANCISCO WASHINGTON, DC www.ropesgray.com

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Bruce S. Manheim, Jr.
(202) 508-4696
bruce.manheim@ropesgray.com

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

Re: Docket No. 2004D-0466, Draft Guidance For Substantiation of Dietary Supplement Claims Made Under the Federal Food, Drug, and Cosmetic Act

Dear Sir or Madam:

On behalf of GlaxoSmithKline Consumer Healthcare ("GSK"), we are submitting comments on the above-referenced draft guidance document governing substantiation of claims made by manufacturers of dietary supplements under Section 403(r)(6) of the Federal Food, Drug, and Cosmetic Act ("FDCA").[1] 21 U.S.C. § 343(r)(6) In these comments, GSK focuses specifically on the issues surrounding substantiation of "structure/function" claims for weight loss products marketed as dietary supplements.[2] GSK believes that it is critically important for FDA to require substantiation for such products since overweight individuals who do not receive effective treatment run the risk of developing serious diseases. As described in more detail below, GSK endorses prompt issuance of a final guidance document on this subject since certain dietary supplement manufacturers are making claims about their products that lack credible scientific substantiation. GSK believes that vigorous and consistent enforcement action against such parties on the basis of stringent standards will not only strengthen protection of the public health but should also be welcomed by responsible parties in the dietary supplement industry.

[1] The FDA published notice of the availability of this guidance document on November 9, 2004. 69 Fed. Reg. 64957. Although the 60 day period for receipt of comments on this draft guidance has expired, GSK respectfully requests FDA to exercise its discretion and consider these comments in connection with finalization of this guidance.

[2] Although GSK's comments in this letter focus on claims for weight loss, these same principles should apply to a wide number of claims for other types of products. Indeed, GSK has previously expressed substantial concerns about the claims that various dietary supplement manufacturers are currently making about dietary supplement products that purport to help smokers quit.

In these comments, GSK initially focuses on key elements in the draft guidance and expresses support for many of these provisions. In this context, GSK provides FDA with additional information and recommendations for certain standards that may help inform an evaluation of substantiation specifically for weight loss claims. GSK then turns to an analysis of the principal comments submitted by representatives of the dietary supplement industry. Based on this review, GSK urges FDA to reject many of these comments since they would fundamentally weaken the substantiation requirement and thereby further expose consumers to false and misleading claims about weight loss supplements. GSK concludes these comments by urging FDA to continue pursuing enforcement actions against manufacturers of weight loss supplements who are currently making unsubstantiated claims about their products. In some cases, these manufacturers continue making claims despite receiving warning letters from FDA finding such statements to be false and misleading under the FDCA.

I. The FDA Should Quickly Finalize the Draft Guidance, and Strengthen Key Elements of Substantiation Still Further, to Ensure Protection and Advancement of the Public Health

The FDA's draft guidance provides an excellent framework for ensuring adequate substantiation of "structure/function" claims for dietary supplements, including claims for weight loss. There is a clear need for written guidance in this area, as DSHEA does not define substantiation and, as noted above, many dietary supplement products claiming weight loss attributes lack credible scientific substantiation. GSK endorses FDA's plan to adopt the FTC's "competent and reliable evidence" standard as the FTC sets a "high bar" and has developed a long track record and series of precedents that are well-understood by the industry. The resulting consistency in enforcement between product labeling and advertising will likewise be a positive outcome, especially in the area of weight loss products, which both agencies have declared to be a high priority. Setting a "high bar" for scientific substantiation will help maintain consumer confidence in these products and prevent consumer fraud and deception.

Overarching Framework: GSK agrees with the overarching framework in the draft guidance: namely, that substantiation for a claim must relate to the specific product and claim; that it be scientifically sound; and that it be adequate in the context of the surrounding body of evidence. In this regard, FDA provides an excellent example in the draft guidance specific to substantiating a claim for weight loss. In "Example Number 2," FDA correctly notes that a dietary supplement claiming to "promote weight loss" would not be substantiated if the only evidence was a 24-hour study showing a small but significant increase in metabolism over placebo, because the hypothetical study did not examine the effect of the ingredient on weight loss directly, and there is no research showing that a short term increase in metabolism would translate into any measurable weight loss.

While FDA presented this example in the context of why the precise claim needs to be studied, the example also speaks to the importance of scientifically credible evidence and the

need to look at the totality of evidence available. GSK similarly agrees that such studies must include the same supplement/ingredient that would be marketed; that the population being studied is similar to the population that would use the product once marketed; and that the claim accurately conveys to consumers the extent, nature, and permanence of the effect achieved. These latter points are particularly important in substantiating claims for weight loss. It is essential that the ingredient be studied in the same patient population as the intended users, particularly patients who wish/need to lose a moderate amount of weight but who do not fall within the "obese" category (thereby rendering the claim a "disease" claim not legally applicable to dietary supplements). It is also essential that the studies adequately document how long it takes to lose weight, how much weight patients can reasonably expect to lose, and what likelihood there is that the patient will gain back all or part of the weight lost after ceasing use of the weight loss product.

Scientific Credibility: GSK agrees that the core of the draft guidance is the need for scientific credibility of the studies being relied upon. GSK agrees with FDA that the "gold standard" is the randomized, double-blind, placebo-controlled study and that, while such evidence may not always be available, that interventional studies of various study designs (e.g., active control studies) are more persuasive than observational studies. Conversely, GSK believes that animal studies (or in vitro studies) alone should not be sufficient to substantiate a claim—at least for weight loss—nor should testimonials or other anecdotal evidence. This is an area where the draft guidance could be strengthened.

For example, while the draft guidance makes clear – particularly in its discussion of example cases – the lesser status and relevance of case reports, anecdotal reports, testimonials, in vitro data, and animal data, GSK believes that the language of the draft guidance is too permissive with regard to these sources of substantiation. Rather, GSK believes that uncontrolled case reports, anecdotal reports, testimonials, in vitro data, and animal data can never substantiate a claim for human clinical effects or benefits, at least with respect to weight loss claims. Furthermore, such data are open to overwhelming bias, and can be manipulated or selectively cited by product sponsors to putatively "substantiate" scientifically unsupportable claims. By stating that such data are "generally" inadequate or "may not be adequate" to substantiate clinical claims, the agency appears to leave the door open and to allow for cases where such evidence might be deemed adequate. That ambiguity, in turn, could enable sponsors to claim substantiation where none exists, and embroil the Agency in numerous disputes.

Moreover, this ambiguity in the wording of the draft guidance may make enforcement actions difficult for the agency to sustain, and may encourage litigation challenging the agency's application of any final guidance. In addition, the ambiguity of the draft guidance, if maintained in the final document, may also affect actions by other parties and institutions that play a role in policing consumer claims (such as the FTC, state attorneys general, and various industry self-policing groups, such as the broadcast networks, the National Advertising Division of the Better

Business Bureau, and others), making it difficult to apply appropriate scientific standards to substantiation of DSHEA claims. Accordingly, GSK urges FDA to revise the language in the final guidance document to make clear that uncontrolled case reports, anecdotal reports, testimonials, in vitro data, and animal data can never be used alone to substantiate a claim, absent qualifying interventional clinical studies.

GSK recognizes the statutory framework governing dietary supplements whereby companies do not have to submit "raw data" to FDA for review. Within this context, GSK agrees with the draft guidance that publication of study results in a peer-reviewed journal would increase its credibility. Similarly, GSK agrees with the draft guidance that replication of results in independently conducted studies adds greatly to the persuasiveness of the evidence as a whole. This is especially critical in the weight loss area where consumers are relying heavily on claims that particular products will improve their health by helping them lose weight and keep the weight off. This is also increasingly important in today's environment where disease prevention is receiving the emphasis it deserves in overall public health. Thus, FDA should properly place greater emphasis on evidence that is replicated in scientifically robust interventional studies and which has been published in a reputable, peer-reviewed scientific journal.

Good Clinical Practices: One gap in the draft guidance concerns the importance of good clinical practices to the reliability of scientific evidence. The draft guidance addresses the nature of evidence required for support of claims under DSHEA, focusing on the kinds of studies that may be considered relevant to such claims. However, even a well-designed study cannot provide reliable and valid scientific evidence if it is not properly conducted, documented, analyzed, and reported. In order to ensure that the kinds of scientific evidence contemplated under the draft guidance are useful, it is essential that studies be conducted using Good Clinical Practices, as specified in guidelines developed by the International Council on Harmonization (ICH) and adopted by FDA. Auditable conformity to agreed-upon standards of rigor, accuracy, and integrity in research is essential to the creation of a reliable and probative scientific record. Therefore, in reviewing any data from controlled clinical trials for dietary supplements, FDA must ensure that sponsors comply with established FDA guidelines on good clinical practices that spell out the standards for study design, sample size, and other trial parameters.[3]

Applying the Guidance to Weight Loss Claims: Finally, in applying this general guidance on substantiation to specific claims for weight loss from dietary supplements, GSK urges the FDA to recognize several important factors. First, studies for weight loss claims for dietary supplements should only include test subjects who have a body mass index (BMI) of less than 30, as persons with a BMI of 30 or more are considered to be obese which would take the study outside the scope of supporting permissible structure/function claims. Study subjects

[3] *See* 62 Fed. Reg. 25692 (May 9, 1997).

should also be drawn from a diverse population, including those of both genders and multiple racial backgrounds. Second, the study endpoints and means of measuring those endpoints should be clearly stated in any study protocol. These endpoints should include both absolute measures (i.e., number of pounds lost) as well as relative measures (e.g., percent of body weight or change in BMI). Third, scientific studies should demonstrate a meaningful level of weight loss. The health benefits patients are generally looking for cannot be achieved by losing a mere two or three pounds. Similarly, the studies should demonstrate that the weight loss can be sustained over a meaningful period of time. Finally, weight loss study protocols need to encompass the important role that diet and exercise play as part of a responsible weight loss regimen. Both the study and controls groups should follow similar diet/exercise regimens so the effect of the dietary supplement can be accurately assessed. As FDA finalizes this guidance, GSK urges the agency to take into account the importance of scientifically sound and replicated study results for weight loss claims.

II. The FDA Should Reject Many of the Comments of the Dietary Supplement Industry Since They Are Not Supported by the Law and Would Undermine Protection of the Public Health

In this section, GSK addresses the principal comments submitted, to date, on the draft guidance document.[4] At the outset, GSK would like to express its support for the comments filed by the American Heart Association ("AHA"). In pertinent part, the AHA indicated that documentation needed to substantiate claims is not clearly specified, and this could lead to abuse by manufacturers. To address this issue, AHA suggested that each section of the guidance should include both good and bad examples for meeting each criterion. AHA also called for increased consumer testing by dietary supplement manufacturers to demonstrate that any claim made for a supplement is clearly understood by the consumer. Furthermore, AHA takes the position that any company submitting a proposal for supplement claims should be required to acknowledge potential adverse effects of different population groups. GSK endorses these recommendations, particularly as they apply to weight loss products, and it urges FDA to incorporate these measures into the final guidance. On the other hand, GSK urges FDA to reject many of the comments submitted by representatives of the dietary supplement industry since they would fundamentally undercut the ability of FDA to ensure that supplement products do not contain false and misleading claims.

[4] As of the date of this filing, comments have been submitted to the docket by the National Nutritional Foods Association; National Association of Chain Drug Stores; Pharmavite; Herbalist and Alchemist, Inc.; American Society for Clinical Pharmacology and Therapeutics; Herb Pharm, Inc.; American Herbal Products Association; National Food Processors Association; Traditional Medicinals, Inc.; Grocery Manufacturers of America; Basic Research, LLP; Standard Process, Inc.; Douglas Kalman; American Heart Association Nutrition Committee; Council for Responsible Nutrition.

Flexibility of Substantiation: A number of comments asserted that FDA's position on substantiation of claims is too narrow and does not allow supplement manufacturers enough flexibility in relying on quality scientific evidence. GSK believes that FDA's definition of claim substantiation, with its close attention to quality evidence, is appropriate and should be enforced. Indeed, the guidance itself provides no firm rules, stating that "there is no pre-established formula" to the number or type of studies required to substantiate a claim. The guidance further states that "there is no general rule for how many studies, or what combination of types of evidence, is sufficient to support a claim." Rather, FDA's position requires claims to be based on competent and reliable scientific evidence, but the way that evidence is obtained or presented is not subject to any strict rules or specific regulatory scheme. FDA is entrusted with ensuring the safety and efficacy of products, and it should not sacrifice these goals for the sake of a perceived need for flexibility where such flexibility already exists.

Traditional Use Claims: FDA should also reject those comments that essentially urged the agency to create an exception for "traditional use" claims – that is, claims which state that a product has been used for a certain purpose without necessarily claiming effectiveness. On this question, the draft guidance states that, while these claims may be accurate, they cannot be objectively evaluated and applied to the consumer who would use the product. GSK believes that FDA's position on traditional use is appropriate and should be enforced. While traditional use claims may arguably be appropriate for certain types of general health products (e.g., perhaps vitamins or minerals with general health utility claims), they have little utility in supplement weight loss claims. That is because such claims are aimed at a serious medical condition linked to disease and often promise a more specific mechanism of action or medical result. While traditional use may be appropriate secondary evidence, it does not and cannot provide an adequate level of scientific evidence on its own. Thus, GSK agrees with FDA's approach to this issue by allowing traditional use claims to serve as additional or background material but not allowing this information alone to substantiate specific claims about dietary supplement products.

Foreign-Based Studies: Finally, several parties claimed that FDA's position on using foreign-based studies to substantiate claims is overly restrictive. Yet, based upon a close reading of the draft guidance, FDA is not necessarily restricting the use of foreign based studies to serve as substantiating evidence for dietary supplement claims. In fact, FDA specifically declares in the draft guidance that "foreign research could be sufficient to substantiate a claim as long as the design and implementation of the foreign research are scientifically sound and the foreign research pertains to the dietary supplement at issue." Accordingly, FDA does not differentiate between foreign and U.S. research, as long as the research supplies valid evidence that applies to the particular supplement and the particular claim. In this context, GSK also notes that several comments suggested that FDA's approach in the guidance document should be consistent with international guidelines. To be sure, FDA may defer to existing standards for substantiation developed by another government agency or other authoritative body. Nothing, however,

requires FDA to accept a lower standard for substantiation because another country uses such a standard. That approach is consistent with FDA's approach to other food and drug products, and dietary supplements should not be treated any differently.

III. The FDA Must Continue to Pursue Aggressive Enforcement Actions Against Manufacturers of Weight Loss Supplements Who Are Making Unsubstantiated Claims About Their Products

Lastly, GSK urges FDA not to wait for completion of the guidance document before continuing enforcement action against certain weight loss supplement products. While GSK fully embraces the draft substantiation guidance, there are a number of dietary supplements currently being marketed with unsubstantiated claims of weight loss. Such claims should not be permitted to stand. That is particularly true since the manufacturers of such products were warned by FDA in its October 22, 2004, advisory letter that the agency would focus resources and attention on enforcing the substantiation requirement against dietary supplement products with "weight loss" claims.[5] GSK commends FDA for following through on that advisory letter with additional warning letters to particular manufacturers making unsubstantiated weight loss claims for their products. Nevertheless, despite those warning letters and others issued by the agency before October 2004, many of these manufacturers continue to make unsubstantiated claims about their products.

Substantiation of Claims on Websites: To date, FDA has issued at least 28 warning letters to manufacturers of weight loss supplements who are making unsubstantiated claims about their products. Most of these letters have focused on the claims being made for products sold on the companies' websites. GSK has followed up on many of these letters. Yet it appears that relatively few companies (eight) have actually taken their products off the market or removed all unsubstantiated claims in response to these warning letters.[6] On the other hand, twenty supplement manufacturers have allowed at least some of their unsubstantiated claims to remain on their websites or have altered the claims in ways that do not fully address the concerns

[5] *See* Advisory Letter to Dietary Supplement Distributors About Unsubstantiated Weight Loss Claims from Joseph Baca, Director, Office of Compliance, Center for Food Safety and Applied Nutrition, Oct. 22, 2004, available at www.cfsan.fda.gov/~dms/wl-ltr26.html

[6] These firms and their respective products are: Getbuf.com (IDS Carb Shuttle), Bionutricals International, Inc. (CarboGetic; Metabo Fat Blocker; Extreme Carb Blocker), Genesis Nutrition (Super Chitosan), Metabolic Nutrition, Inc. (Liposin), Net Unique Inc. (Ultra Carbo Blocker 3000), Certified Natural Laboratories, Inc. (Fatblack X-TREME; Extreme Fat Burner; Advantage Carb Blocker), R.P.M. Worldwide (Starch Blocker 1000 Ultra Carb Blocker), and Proper-Health.com/Power-Plus.org (Metabo FatBlocker; Extreme Carb Blocker).

raised by FDA.[7] Thus, many of the firms that have received warning letters from FDA are flouting them. FDA needs to follow through on many of its warning letters and continue to pursue action against weight loss supplement manufacturers making unsubstantiated claims about their products over the Internet.

Substantiation of Claims at the Retail Level: At the same time, GSK urges FDA to bring a renewed focus on substantiation of claims for weight loss products sold at the retail level. The FDA indicated in its Regulatory Strategy for Implementation of the Dietary Supplement Health and Education Act that it would more closely scrutinize products in the marketplace and that, initially, those efforts would target products promoted for weight loss.[8] GSK applauds FDA for committing to such action since an increasing number of weight loss supplements with unsubstantiated claims appear to be appearing on the shelves. Indeed, based on a brief assessment of weight loss supplements sold at two major pharmacy chains (CVS and Walmart), GSK found that at a number of dietary supplements are currently being sold with unsubstantiated claims of weight loss. In some cases, such products are being sold with precisely the types of claims that the FTC and FDA had previously identified as false and misleading.[9] In fact, several

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[7] These firms and their respective products include: Top of the World Distributors (Starch Blocker 1000), Pro Star International, Inc. (Lean Image Carb Blocker), Weightlossguide.com (Zone Fat Blocker), VitaMaker.com (TrimSpa Carb Blocker; TrimSpa Fat Blocker), Williams Vitamins (Super Starch Blocker 1000), Vitality Products Co., Inc. (Eternal Youth Age Reversal Formula Human Growth Hormone Releaser), Physician's Choice Inc. (Super Lipo Blocker, Super Slim), American Products (ChitoSlim; Ultimate Slim Ephedra-Free), Tiffin International, Inc. (Ultra Block 2000 Plus C; Ultra Carbo Blocker 2000), New You Labs (Metabo Fat Blocker/Metabo UltraMax), M.R.S. Marketing (Ultra Carbo Blocker 3000), eVitamins.com (F Block Chitosan Caps; Chitosan 500mg), Ecommerce Transactions, LLC (Dream Shape), Better Bodz (InShape Dreamshape), VitaminLab (Carb Blocker Triple Action Formula; Fat Blocker-Chitosan Complex), Cytodyne LLC (Xenadrine CarboCurb), Nature's Sunshine Products (Carbo Grabbers; Fat Grabbers), Reliant World Products (Miracle Tab), Tao of Herbs (Now Phase 2; Now Chitosan w/ Chromium), and Irwin Naturals (Maximum Strength Phase 2 Carb-Blocker).

[8] *See* "Regulatory Strategy for the Further Implementation and Enforcement of the Dietary Supplement Health and Education Act of 1994," Center for Food Safety and Applied Nutrition, November 2004; available at www.cfsan.fda.gov/~dms/ds3strat.html.

[9] The FTC identified these types of claims in its December 2003 staff report. *See* "Deception in Weight Loss Advertising Workshop: Seizing Opportunities and Building Partnerships to Stop Weight Loss Fraud, Federal Trade Commission Staff Report, December 2003. Available at http://www.ftc.gov/os/2003/12/031209weightlossrpt.pdf. The FDA referred to those claims in its October 2004 advisory letter to the industry.

of these products are on the shelves despite warning letters from FDA to the manufacturers of such products challenging substantiation of their statements on their respective websites.[10]

Accordingly, as FDA finalizes this guidance, the agency must follow through on its commitment to addressing unsubstantiated weight loss claims including, where necessary, initiating court action under the FDCA to remove such products from the market. 21 U.S.C. §§ 332, 334. Such action is fully consistent with the policies set out at § 120.500 of FDA's Compliance Policy Guide governing the timing and nature of enforcement against health fraud products.[11] Consumers remain particularly susceptible to products making weight loss claims and they should not use products with unsubstantiated claims when scientifically proven products are available. This is especially important in light of the increasingly large body of evidence indicating that weight loss is linked to a reduced risk of chronic diseases such as diabetes, heart disease, and obesity. Yet, by creating false hope through unsubstantiated claims for weight loss products sold both at the retail level and through the Internet, manufacturers of dietary supplements are essentially denying or delaying effective treatment of such diseases.

IV. Conclusion

In sum, GSK strongly supports FDA's efforts to develop further guidance on what evidence is needed to substantiate a structure/function claim on dietary supplements. GSK also commends FDA for affirmatively bringing this approach to substantiation in line with that taken for many years by the FTC. The FTC's standard of "competent and reliable evidence" has a long track record of application by the FTC and should properly be applied to dietary supplement label claims as well.[12] As FDA finalizes this guidance, it should continue to collaborate closely with the FTC in its ongoing enforcement efforts against marketers of dietary supplements making unsubstantiated weight loss claims. Indeed, GSK believes that it is critically important for both agencies to require substantiation for such products since overweight individuals who do

[10] The manufacturers of Carb Intercept and Trimspa previously received warning letters from FDA in April 2004 regarding unsubstantiated claims on their websites. Yet, these products are currently being sold at the retail level with the same claims, albeit by different distributors. Other products currently being sold at the retail level that trigger the FTC/FDA factors include Carb Cutter, CVS Starch Blocker, Mega-G, Relacore, and Starch Away.

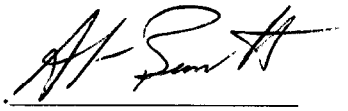
[11] *See* "Health Fraud – Factors In Considering Regulatory Action." CPG 7150.10 is available at http://www.fda.gov/ora/compliance_ref//cpg/cpggenl/cpg120-500.html.

[12] *See e.g.*, "FTC Policy Statement Regarding Advertising Substantiation" (July 27, 1984); "Dietary Supplements: An Advertising Guide for Industry" (April 2001); FTC comments to FDA on the Structure/Function Proposed rule, Docket No. 98N-0044, August 27, 1998.

not receive effective treatment run a higher risk of becoming obese or developing other serious diseases such as diabetes and heart disease.

Thank you for your consideration of these comments.

Sincerely,



Alan Bennett
Bruce S. Manheim, Jr.
Ropes & Gray LLP
One Metro Center
700 12th Street, N.W., Suite 900
Washington, D.C. 20005-3948
(202) 508-4600

Attorneys for GlaxoSmithKline Consumer Healthcare, LP

Copies to:

Robert Brackett, Ph.D., Director, CFSAN
Michael Landa, Deputy Director, Regulatory Affairs, CFSAN
Barbara Schneeman, Ph.D., Director, Office of Nutritional Products, Labeling, and Dietary Supplements, CFSAN
Vickey Lutwak, Office of Nutritional Products, Labeling, and Dietary Supplements, CFSAN
Susan Walker, M.D., Director, Div. of Dietary Supplement Programs, CFSAN
Joseph Baca, Director, Office of Compliance, CFSAN